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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/811,138	03/29/2004	Sylvia Daunert	50229-421	8471

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/811,138	DAUNERT ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 14-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group X, claims 12-13, in the reply filed on October 26, 2006 is acknowledged. Claims 1-11 and 14-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. No claims have been amended, canceled or added. Accordingly, claims 12-13 are examined on the merits herewith.

Applicants have traversed the restriction requirement, asserting that it would not be an undue burden for Examiner to search and examine nine different claimed proteins. Applicants refer to an O.G. notice from 1996 that allowed for the examination of up to ten different polynucleotide sequences.

In reply, it is an enormous burden, a nine-fold burden, for any examiner to search and examine nine different protein sequences. As explained in the previous Office action, each protein is a different and separate invention, because each sequence must be searched and examined separately, and searching each sequence produces eight sets of results that must be considered. Each examiner has an extremely limited and ever diminishing amount of time to spend on each case, biotechnology cases are of ever-increasing size, and a substantial backlog exists with each examiner and at the searching facility. Filing a very large number of sequences and inventions in one application is elective on the part of Applicants, and Applicants' subsequent need to file divisional applications is not a criterion for restriction. Each of Applicants' sequences contains a mutation at a different position, and each mutation must be addressed individually. Nine different sequences require nine different searches, because a mutation at one amino position does not render obvious a mutation at a different amino acid

position, and because each mutation must be searched separately. Separate searches are required by the database searching software, and, additionally, a text/key word search is performed for each claimed mutation.

As for the O.G. notice, this was written in early days of EST's to cover polynucleotide sequences, at a time when the searchable databases were much smaller than they are today and the backlog at the Office, including the searching facility, was much smaller. This notice pertains to polynucleotide sequences, not protein sequences.

As previously discussed, current Office policy is that one protein sequence will be searched and examined in each application. Accordingly, the restriction requirement is maintained and is made final.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO: 3 in which position numbers 347-348 are mutated from AT to GG or TC or TT to produce the Y-to-W or Y-to-F amino acid mutation (one or two point mutations in this codon), does not reasonably provide enablement for any polynucleotide that is "capable" of hybridizing to SEQ ID NO: 3 under stringent conditions and that encodes a protein that is "capable" of binding coelenterazine and oxygen and emitting light and that has a W or F at amino acid position 82 of SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The

protein of SEQ ID NO: 4 and its variants with W or F at position 82 are functional aequorins, and the specification does not disclose, apart from the claimed mutations, how else the polynucleotide and polypeptide sequences may be mutated to produce the invention of claims 12-13.

The factors to be considered in determining whether or not undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a

correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1.Breadth of the claims.

The claims are very broad because they recite any polynucleotide that is capable of hybridizing to SEQ ID NO: 3 under stringent conditions and that encodes a protein that is capable of binding coelenterazine and oxygen and emitting light and that has a W or F at amino acid position 82 of SEQ ID NO: 4.

2. The nature of the invention.

The invention is designed to provide a novel aequorin protein.

3. The state of prior art.

Bryan (US 5,876,995) discloses a polynucleotide that encodes an aequorin that binds coelenterazine and oxygen and emits light (see SEQ ID NO: 7, cols. 113-116; cols. 19-23, Aequorin and related proteins). This polynucleotide differs from SEQ ID NO: 3 by three nucleotides (see Result 1 from a search in the issued patents protein database, an alignment of Applicants' SEQ ID NO: 4 with SEQ ID NO: 7 of Bryan). The codon for S at amino acid positions 145 and 152 (AGC) is TCG in Bryan's sequence. The codon for amino acid position

82 (TGG, TTT or TTC) is TAT in Bryan's sequence. Thus, Bryan's polynucleotide sequence has 99.5% sequence identity to Applicants' claimed sequence.

4. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

5. The level of predictability in the art.

Because it is not known how to vary SEQ ID NO: 3 so that the encoded protein will have a W or F mutation at amino position 82, so that the encoded protein will be capable of binding coelenterazine and oxygen and emit light, and so that the variant of SEQ ID NO: 3, mutated at an unlimited number of positions (additions, deletions and substitutions) will hybridize under stringent conditions to SEQ ID NO: 3, the specification needs to have more detail as to how to make and use the invention. As discussed above, no such polynucleotides apart from SEQ ID NO: 3 are disclosed, and the specification does not define stringent conditions. Page 18 of the specification discusses hybridization and washing conditions. But the washing conditions are more important than the hybridization conditions for determining what binds to a target DNA at the end of the experiment, and Applicants do not disclose washing under stringent conditions. Applicants use hybridization conditions that one of skill in the art would consider to be of high stringency. But, the room-temperature washing does not maintain stringent conditions. Thus, the DNA or RNA molecules that hybridize according to Applicants' protocol are not those that hybridize under stringent conditions. Because the prior art and the instant specification do not disclose any polynucleotide that is capable of hybridizing to SEQ ID NO: 3 under stringent conditions and that encodes a protein that is capable of binding coelenterazine and oxygen and emitting light and that has a W or F at amino acid position 82 of SEQ ID NO: 4, apart from SEQ ID NO: 3, it cannot be predicted that any other polynucleotide that is a variant of SEQ ID NO: 3

would encode a protein having all of the claimed functional properties.

6. The amount of guidance present.

Applicants have not provided any guidance for preparing any polynucleotide that is capable of hybridizing to SEQ ID NO: 3 under stringent conditions and that encodes a protein that is capable of binding coelenterazine and oxygen and emitting light and that has a W or F at amino acid position 82 of SEQ ID NO: 4, apart from SEQ ID NO: 3.

7. The existence of working examples.

The specification does not contain any working examples related to the claimed mutation of SEQ ID NO: 3, i.e., related to using a protein with a W or F mutation at position 82.

8. The quantity of experimentation necessary.

To prove that polynucleotides exist that are capable of hybridizing to SEQ ID NO: 3 under stringent conditions and that encode proteins that are capable of binding coelenterazine and oxygen and emitting light and that have a W or F at amino acid position 82 of SEQ ID NO: 4, apart from the polynucleotide of SEQ ID NO: 3, many experiments would have to be conducted under a wide range of conditions. In these experiments, many different proteins encoded by many different variants of SEQ ID NO: 3 would have to be prepared and tested to see that each protein has the functional properties of an aqueorin, with W or F at position 82, and that each polynucleotide encoding each of these proteins hybridizes to SEQ ID NO: 3 under stringent conditions. Each variant of SEQ ID NO: 3, in addition to the required mutations at the codon of nucleic acid positions 347-348, would have to have a different number of nucleotides deleted and/or added and/or substituted. Many classes of variant polynucleotides would have to be prepared, those with nucleotides: deleted and added, deleted and substituted, added and substituted, and deleted, added and substituted. For each class, a large number of sets of polynucleotides would have to be prepared, each set having a different of nucleotides changed

from the original SEQ ID NO: 3. For each set, a large number of subsets would have to be prepared, each subset having a different permutation of nucleotide positions changed. For each subset, a large number of members would have to be prepared, each member in each subset having a different group of nucleotides at the altered positions. For all polynucleotides that hybridize under stringent conditions to SEQ ID NO: 3, all the encoded proteins would have to be shown to have the functional properties of an aequorin.

These types of experiments and data are missing from the specification. A great deal of guidance is needed to establish that a genus of polynucleotides that are capable of hybridizing to SEQ ID NO: 3 under stringent conditions and that encode proteins that are capable of binding coelenterazine and oxygen and emitting light and that have a W or F at amino acid position 82 of SEQ ID NO: 4 can be made, apart from SEQ ID NO: 3, because this genus is claimed, and only one species is disclosed. Even if one additional species could be made and identified by random, trial-and-error experimentation, without a very large amount of data, such a result would not allow one of skill in the art to expect that a second undisclosed species exists.

Therefore, the claims fail to satisfy the enablement requirement.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the term "stringent conditions." As discussed above, the specification does not define or disclose stringent conditions, nor does it disclose any polynucleotides that bind under stringent conditions to SEQ ID NO: 3, regardless of what

proteins they encode. Appropriate correction is required. The claims may be amended to recite polynucleotides encoding a protein that is a variant of SEQ ID NO: 4 in which position 82 is W of F.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652

rk/2006-11-21

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